BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.131 Pharmacogenetic Testing for Pain Management

### Effective Policy Date: April 1, 2023

### Original Policy Date: June 2015

### Related Policies:

2.04.110 - Genetic Testing for Diagnosis and Management of Mental Health Conditions
2.04.38 - Cytochrome P450 Genotype-Guided Treatment Strategy

## Pharmacogenetic Testing for Pain Management

### Description

## Description

While multiple pharmacologic therapies are available for the management of acute and chronic pain, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain, and in adverse events. Testing for genetic variants that are relevant to pharmacokinetics or pharmacodynamics of analgesics may assist in selecting and dosing drugs affected by these genetic variants.

Genetic factors may contribute to a range of aspects of pain and pain control, including predisposition to conditions that lead to pain, pain perception, and the development of comorbid conditions that may affect pain perception. Currently available genetic tests relevant to pain management assess single-nucleotide variants (SNVs) in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes.

Genes related to these clinical scenarios include, broadly speaking, those involved in neurotransmitter uptake, clearance, and reception; opioid reception; and hepatic drug metabolism. Panels of genetic tests have been developed and proposed for use in the management of pain. Genes identified as being relevant to pain management are summarized in Table 1.

### Table 1. Genes Relevant to Pain Management

| Gene | Locus | Gene Product Function |
|---|---|---|
| *5HT2C* (serotonin receptor gene) | Xq23 | 1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine |
| *5HT2A* (serotonin receptor gene) | 13q14-21 | Another serotonin receptor subtype |
| *SLC6A4* (serotonin transporter gene) | 17q11.2 | Clears serotonin metabolites from synaptic spaces in the CNS |
| *DRD1* (dopamine receptor gene) | 5q35.2 | G-protein-coupled receptors that have dopamine as their ligands |
| *DRD2* (dopamine receptor gene) | 11q23.2 | |
| *DRD4* (dopamine receptor gene) | 11p15.5 | |
| *DAT1* or *SLC6A3* (dopamine transporter gene) | 5p15.33 | Mediates dopamine reuptake from synaptic spaces in the CNS |
| *DBH* (dopamine beta-hydroxylase gene) | 9q34.2 | Catalyzes the hydroxylase of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons |
| *COMT* (catechol *O*-methyl-transferase gene) | 22q11.21 | Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine |
| *MTHFR* (methylenetetrahydrofolate reductase gene) | 1p36.22 | Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters |
| GABA A receptor gene | 5q34 | Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter |
| *OPRM1*(μ-opioid receptors gene) | 6q25.2 | G-protein coupled receptor that is primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone |
| *OPRK1* (κ-opioid receptor gene) | 8q11.23 | Binds the natural ligand dynorphin and synthetic ligands |
| *UGT2B15* (uridine diphosphate glycosyltransferase 2 family, member 15) | 4q13.2 | Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds |
| Cytochrome p450 genes | | Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics |
| *CYP2D6* | 22q13.2 | |
| *CYP2C19* | 10q23.33 | |
| *CYP2C9* | 10q23.33 | |
| *CYP3A4* | 7q22.1 | |
| *CYP2B6* | 19q13.2 | |
| *CYP1A2* | 15q24.1 | |

CNS: central nervous system; CYP: cytochrome P450;GABA: g-aminobutyric acid; UDP: uridine diphosphate glycosyltransferase.

## OBJECTIVE

The objective of this evidence review is to determine whether the use of genetic testing to manage patients with acute or chronic pain improves the net health outcome.

# POLICY STATEMENT

Genetic testing for pain management is considered **investigational** for all indications (see Policy Guidelines section).

# POLICY GUIDELINES

This policy does not address testing limited to cytochrome p450 genotyping, which is addressed in evidence review 2.04.38. This policy also does not address testing for congenital insensitivity to pain.

Commercially available genetic tests for pain management consist of panels of single-nucleotide variants (SNVs) or (less commonly) individual SNV testing. SNVs implicated in pain management include the following (see also Table 1):

- *5HT2C* (serotonin receptor gene)
- *5HT2A* (serotonin receptor gene)
- *SLC6A4* (serotonin transporter gene)
- *DRD1* (dopamine receptor gene)
- *DRD2* (dopamine receptor gene)
- *DRD4* (dopamine receptor gene)
- *DAT1* or *SLC6A3* (dopamine transporter gene)
- *DBH* (dopamine beta-hydroxylase gene)
- *COMT* (catechol *O*-methyltransferase gene)
- *MTHFR* (methylenetetrahydrofolate reductase gene)
- γ-aminobutyric acid (GABA) A receptor gene
- *OPRM1*(μ-opioid receptor gene)
- *OPRK1* (κ-opioid receptor gene)
- *UGT2B15* (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome p450 genes: *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, *CYP2B6*, *CYP1A2*.

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Some plans may have contract or benefit exclusions for genetic testing.

# FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The OmeCare OmePainMeds panel, the Millennium PGT (Pain Management) panel, and YouScript Analgesic panel are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

No genetic tests approved by the FDA for pain management were identified.

Of note, in February 2020, the FDA expressed "concerns with firms offering genetic tests making claims about how to use the genetic test results to manage medication treatment that are not supported by recommendations in the FDA-approved drug labeling or other scientific evidence".[3,] Due to these concerns, the FDA announced a collaboration between the FDA"s Center for Devices and Radiological Health and Center for Drug Evaluation and Research intended to provide the agency"s view of the state of the current science in pharmacogenetics. This collaborative effort includes a web resource[4,] that describes "some of the gene-drug interactions for which the FDA believes there is sufficient scientific evidence to support the described associations between certain genetic variants, or genetic variant-inferred phenotypes, and altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events."

# RATIONALE

## Summary of Evidence

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a hybrid implementation-effectiveness randomized trial, a single-blind randomized trial, a prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain, and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The hybrid randomized trial concluded that preemptive CYP2D6-guided opioid selection is feasible in an elective surgery setting and that this approach may decrease postoperative opioid utilization with similar pain control compared to usual care; however, these results were only exploratory in nature. The single-blind randomized trial similarly concluded that postoperative opioid prescription guided by genetic results may improve pain control and reduce opioid consumption compared to usual care. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach and found a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Academy of Neurology

In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic noncancer pain.[14,] Regarding pharmacogenetic testing, the guidelines stated that genotyping to determine whether the response to opioid therapy can or should be more individualized is an emerging issue that will "require critical original research to determine effectiveness and appropriateness of use."

## Clinical Pharmacogenomics Implementation Consortium

The Clinical Pharmacogenomics Implementation Consortium (2020) published a guideline for cytochrome P450 (CYP) 2C9 and nonsteroidal anti-inflammatory drugs (NSAIDs), which was developed to provide interpretation of CYP2C9 genotype tests so that the results could potentially guide dosing and/or appropriate NSAID use.[15,] The guideline notes that CYP2C9 genotyping information may provide an opportunity "to prescribe NSAIDs for acute or chronic pain conditions at genetically-informed doses to limit long-term drug exposure and secondary adverse events for patients who may be at increased risk." However, the authors also acknowledge that "while traditional pharmacogenetic studies have provided evidence associating common CYP2C9 genetic variation with NSAID pharmacokinetics, there is sparse prospective evidence showing that genetically-guided NSAID prescribing improves clinical outcomes."

In 2021, the Consortium published an updated guideline for CYP2D6, μ-opioid receptor gene 1 (*OPRM1*), and catechol *O*-methyl-transferase (*COMT*) genotypes and select opioid therapy.[16,] These recommendations state that codeine and tramadol should be avoided in CYP2D6 poor metabolizers due to diminished efficacy and in ultra-rapid metabolizers due to toxicity potential. In both situations, if opioid use is warranted, a non-codeine opioid should be considered. Regarding hydrocodone, there is insufficient evidence and confidence to provide a recommendation to guide clinical practice for CYP2D6 ultra-rapid metabolizers. For CYP2D6 poor metabolizers, the use of hydrocodone labeled age- or weight-specific dosing is recommended; however, if no response is observed and opioid use is warranted, a non-codeine and non-tramadol opioid can be used. There is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone or methadone based on CYP2D6 genotype. Additionally, there are no therapeutic recommendations for dosing opioids based on either *OPRM1*or *COMT*genotype.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

## REFERENCES


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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| June 2015 | New policy | Policy created with literature review through December 2, 2014. Pharmacogenetic testing for pain management is considered investigational for all indications. |
| March 2019 | Replace policy | Policy updated with literature review through September 4, 2018; no references added. Policy statement unchanged. |
| March 2020 | Replace policy | Policy updated with literature review through October 15, 2019; reference added. Policy statement unchanged. |
| March 2021 | Replace policy | Policy updated with literature review through September 21, 2020; references added. Policy statement unchanged. |
| March 2022 | Replace policy | Policy updated with literature review through September 14, 2021; references added. Policy statement unchanged. |
| March 2023 | Replace policy | Policy updated with literature review through September 23, 2022; reference added. Policy statement unchanged. |